# Evaluation of Children with Recurrent Fever

## Tekrarlayan Ateşi Olan Çocukların Değerlendirilmesi



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**Özet**

Amaç: Çocuklarda tekrarlayan ateş hakkında bilgiler kısıtlıdır. Bu çalışma ile tekrarlayan ateş yakınması olan çocuk hastaların değerlendirilmesi amaçlanmıştır. Gereç ve Yöntem: Çalışmaya sık ateşlenme yakınması olan 138 hasta dahil edilmiştir. Yılda 12 ateşli atak 'reküren ateş' için sınır değer kabul edilmiştir. Yılda ≤12 atak geçirenler Grup I, >12 atak geçirenler Grup II içine dahil edilmiştir. Her iki grup demografik verileri, semptomları, klinik ve laboratuvar bulguları açısından karşılaştırılmıştır. Tüm çocuklar iki yıl süreyle tanı amaçlı takip edilmişlerdir. Bulgular: Belirlenen kritere göre hastaların %39.1'inde (n=54) reküren ateş saptanmıştır. Grup I'deki çocuklarda hapşırık daha sıkken, Grup II'dekilerde kusma daha sıktır (sırasıyla p=0.05 ve p=0.02). Grup I'dekiler, Grup II'deki çocuklara göre atakları kış aylarında daha sık görmüşlerdir (p=0.03). Yaş, cinsiyet, diğer semptomlar, fizik inceleme bulguları, kreşe/okula gitme gibi parametreler açısından iki grup arasında fark saptanmamıştır. Grup II'deki çocukların daha yüksek C-reaktif protein düzeyleri olduğu görülmüştür (p=0.001). Diğer laboratuvar parametreleri açısından fark bulunmamıştır. İki yılın sonunda Grup II'de birer hastada hastada Ailevi Akdeniz Ateşi sendromu ve immünglobulin G2 subgrup eksikliği saptanırken, Grup I'deki 1 hastada Periyodik ateş, aftöz stomatit, farenjit, adenit sendromu tanısı konulmuştur. Tartışma: Ayda bir kez ateşli atak geçiren çocukların araştırılması ayırt edici olmayabilir. Bu hastalarda ateşli atak sayısına göre değerlendirme yerine uzun süreli klinik takip uygun tanı ve tedavi yönteminin saptanması açısından daha uygun olabilir.

**Anahtar Kelimeler**

Çocuk; C-Reaktif Protein; Enfeksiyon; Sık Ateşlenme; Tekrarlayan Ateş

**Abstract**

Aim: Data on recurrent fever in children is limited. The aim of this study is to evaluate the children with this common symptom. Material and Method: We enrolled 138 patients with frequent fever. Twelve febrile episodes/year was determined as the cut-off for "recurrent fever". Children with ≤12 and >12 febrile episodes/year were included in Group I and Group II, respectively. Their demographic data, symptoms, and clinical and laboratory findings were compared. All children were followed for two years for definitive diagnosis. Results: Fifty-four (39.1%) children experienced recurrent fever according to our criteria. Group I children experienced more frequent sneezing, whereas Group II children experienced more frequent vomiting compared to the other group (p=0.05 and p=0.02, respectively). Febrile episodes were seen more frequently in the winter season in Group I compared to Group II (p=0.03). Age, sex, other clinical symptoms, physical examination findings, and attendance at day care center/school in two groups were not different. Group II children had higher C-reactive protein levels (p=0.001). There was no difference in other laboratory parameters between the two groups. After two years, two patients in Group II were diagnosed with Familial Mediterranean Fever syndrome and immunoglobulin-G2 subgroup deficiency, while one patient in Group I was diagnosed with periodic fever, aphtous stomatitis, pharyngitis, and adenitis syndrome. Discussion: To investigate only those children presenting with fever episodes of at least once a month may not be discriminative. To construct an algorithm for diagnosis and treatment, it would be better to follow recurrent fever patients for a longer duration rather than initially categorizing them according to the number of episodes.

**Keywords**

Children; C-Reactive Protein; Infection; Frequent Fever; Recurrent Fever

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## Introduction

Fever is a beneficial physiological response to many infectious and noninfectious illnesses. It is a very useful sign of illness, but it also evokes inordinate fear and anxiety, especially when it recurs [1]. Recurrent or periodic fever is a fairly common complaint in children, but the literature on this topic is sparse and largely confined to case reports or small case series [2]. Either with regular or irregular intervals, fever may recur as a result of one or more factors, particularly fluctuations in the clinical course of a disease or recurrent diseases of the same organ system at different times or in different recurrent diseases that may involve different organ systems [2-4]. Recurrent fever results most often from infectious diseases, but may also result from congenital immune defects, multifactorial inflammatory diseases, autoinflammatory disorders, and neoplastic diseases [5]. However, there are a number of misconceptions and inaccurate approaches to treatment management regarding fever and recurrent fever in children [6]. For example, the protocol for differential diagnosis and workup of children with recurrent fever is often similar to that used for children with prolonged fever of unknown origin [2].

However, the approach to workup of children with recurrent fever needs to be evaluated thoughtfully and in a more focused way, rather than being based solely on batteries of tests [1]. Patients with recurrent fever present with a history of multiple episodes of fever, so they usually have many visits to primary care providers or emergency rooms where nonspecific diagnoses have been made and antimicrobial therapy may have been prescribed [7].

It is important to generate a differential diagnosis specifically for the child with recurrent fever and to outline a rational approach to workup of these children. Therefore we investigated the difference of some parameters between the children who had 12 or fewer fever episodes per year and those with more than 12. In this way, this study aimed to (a) detect the frequency of fever episodes of patients who present to outpatient clinics complaining of frequent fever and the accompanying symptoms of those febrile episodes, and (b) assess the utility and efficacy of laboratory tests in identifying the cause(s) of fever.

## Material and Method

### *Patient selection and definitions*

We conducted a prospective study with patients younger than 18 years old who had a complaint of recurrent fever. The medical records of each patient were reviewed. The children with concurrent history of trauma or known diagnosis of immunodeficiency, chronic pulmonary disease, collagen vascular disease, or any other systemic disorders were excluded. The included patients were seen in outpatient clinics.

After informed consent from the legal guardians, data including age, sex, number of febrile episodes in the previous year, mean duration of febrile episodes, frequency of symptoms accompanying febrile episodes (i.e., oral ulcers, cough, sore throat, rhinorrhea, sneezing, postnasal discharge, skin eruptions, lymphadenopathy, diarrhea, vomiting, abdominal pain, chest pain, genital ulcers, and complaints about joints and the neurological system), attendance at school or day care centers, and seasonal occurrence of febrile episodes was prospectively collected. All febrile participants underwent physical examinations as advised in the literature [2, 4]. The local ethics committee approved the study.

All patients included in the study were followed and checked for two years in order to reach a definitive diagnosis.

### *Laboratory analysis*

Laboratory tests including white blood cell count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen levels, liver and kidney function tests ([LFT] and [KFT]), and quantitative immunoglobulins (IgA, IgG, and IgM) were performed. Urinary culture was done for all patients. Throat culture was done in patients older than three years with any positive findings related to bacterial tonsillitis/pharyngitis. Blood cultures were planned for patients who experienced febrile episodes of ≥7 days or patients who appeared sick, but no blood culture was performed. Laboratory tests for rheumatological etiology were carried out if the patient had compatible clinical indications. The need for treatment options was also recorded. The same pediatrician reviewed all patients' charts.

Fever was defined as a temperature of ≥ 37.8°C [8]. We arbitrarily defined recurrent fever as 12 or more episodes of fever in the last 12-month period, and with an interval of at least seven days between febrile episodes. The children were divided into two groups according to the number of febrile attacks per year in order to compare demographic features, symptoms, clinical, and laboratory findings. Patients who had experienced ≤12 febrile episodes were included in Group I while those who had experienced >12 febrile episodes were included in Group II.

### *Statistical Analysis*

Data were analyzed using the SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to summarize the participants' baseline characteristics, including means, standard deviations (SDs), and medians (ranges) for continuous variables, and frequency distributions for categorical variables. The chi-squared and Fischer exact tests were used for comparisons of categorical variables. The normality of quantitative variables was tested by Kolmogorov–Smirnov test. For continuous variables, we used the independent-groups t test for normally distributed variables or the nonparametric Mann–Whitney U test if the normality assumption was violated. In all analyses, 2-tailed p-values ≤ 0.05 were regarded as statistically significant.

## Results

During the study period, a total of 186 children were admitted to outpatient clinics with the complaint of recurrent fever. Of these 186 pediatric patients, 138 were enrolled in the study. Forty eight children with recurrent fever with any underlying diseases or chronic conditions (known immunodeficiency, rheumatological, pulmonary, and cardiovascular diseases) were excluded from the study. None of the patients were hospitalized. According to our cut-off point of 12 febrile episodes in a year, 84 (60.9%) and 54 (39.1%) of the patients were included in Group I and Group II, respectively. The most frequently encountered ranges of fever episodes per year were 5-8 episodes (n=35, 25.3%) and 9-12 episodes (n=35, 25.3%) (Figure 1). The me-

dian age of the 138 patients was 37.5 (range 9 to 129) months and the male-to-female ratio was 1.9 (91 boys and 47 girls). Statistically significant differences were not found in terms of patients' age (p=0.91) and gender (p=0.85).

By the end of the two year follow-up, one patient had been diagnosed with FMF (Familial Mediterranean Fever) and one patient had been diagnosed with IgG2 (immunoglobulin G2 subgroup) deficiency in Group II, while PFAPA (periodic fever, aphtous stomatitis, pharyngitis, and adenitis) was diagnosed in one patient in Group I.

At a statistically significant level, children in Group I experienced sneezing more frequently compared to Group II, whereas children in Group II experienced vomiting more frequently compared to Group I (p=0.05 and p=0.02, respectively) (Figure 2). Febrile episodes were shown to be significantly more frequent in winter season in Group I compared to Group II (p=0.03) (Figure 3). Statistically significant difference was not found regarding attendance at day care/school between Groups I and II (p=0.79).

There were no statistically significant differences between the groups regarding any physical examination findings (Table 1). CRP level was significantly higher in children in Group II compared to the children in Group I (p=0.001) (Table 1). Although blood culture was not performed for any patient, throat culture was performed for 14 patients who presented with tonsillopharyngitis. One throat culture in each group was positive for group A beta hemolytic streptococcus. Among all the patients, 4 had positive urine cultures, three cultures revealed E. Coli and one culture revealed Candida albicans; two had abnormal LFT results and none had abnormal KFT results.

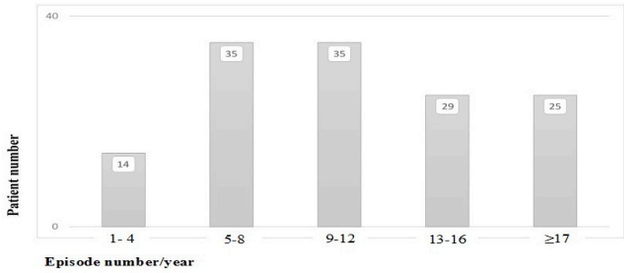


Figure 1. The distribution of fever episode frequencies

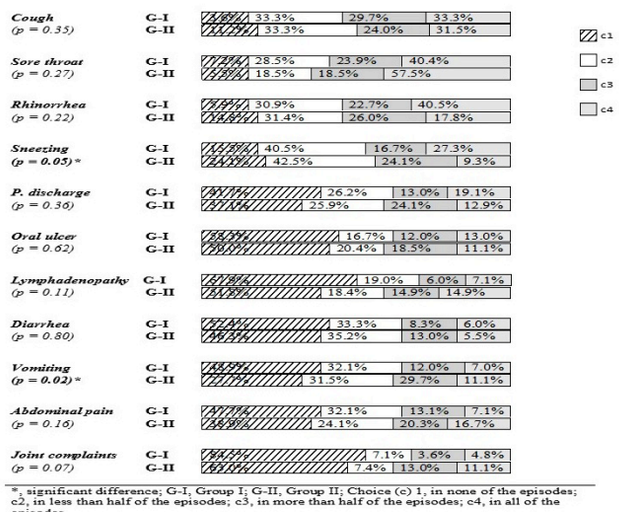


Figure 2. The relationship between the fever frequency and some of the clinical symptoms

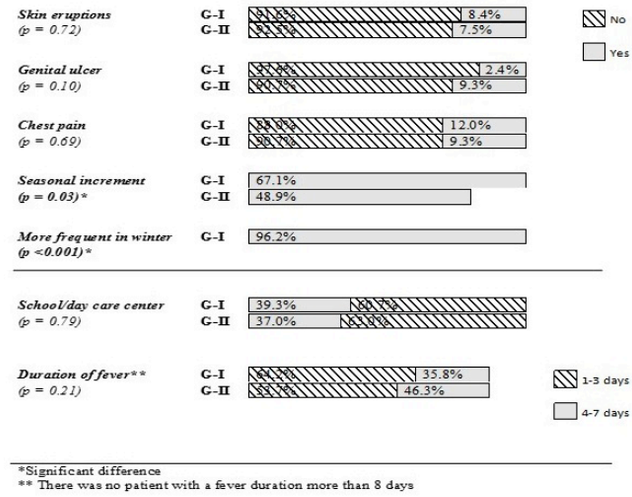


Figure 3. Relationship between the fever frequency and some of the patient characteristics and clinical symptoms

Table 1. Patients' physical examination and laboratory findings

| Physical examination findings | Group I (n=84) n (%) | Group II (n=54) n (%) | p |
|---|---|---|---|
| Growth retardation | 2 (2.4) | 2 (3.7) | 0.64a |
| Tonsillopharyngitis | 50 (59.5) | 38 (70.4) | 0.19a |
| Sinusitis | 4 (4.8) | 2 (3.7) | 1.00a |
| Otitis media | 15 (17.9) | 7 (13.0) | 0.44a |
| Dental carries | 8 (9.5) | 4 (7.4) | 0.76a |
| Oral ulcers | 2 (2.4) | 5 (9.2) | 0.11a |
| Lymphadenopathy | 17 (20.2) | 17 (31.4) | 0.13a |
| Cardiac murmur | 5 (6.0) | 2 (3.7) | 0.70a |
| Abdominal sensitivity | 1 (1.2) | 2 (3.7) | 0.56a |
| Laboratory Findings | | | |
| WBC [103/μL; median (IQR)] | 9100 (7100-13200) | 10650 (8200-13300) | 0.14b |
| ESR [mm/h; median (IQR)] | 14 (9-27) | 18 (13-33) | 0.06b |
| CRP [mg/dl; median (IQR)] | 1.08 (0.24-3.23) | 2.44 (0.82-6.17) | 0.001b** |
| Fibrinogen [mg/dL; mean±SD] | 363.8±99.6 | 397.1±119.0 | 0.08c |
| IgA [mg/dL; mean±SD] | 90.3±57.7 | 106.8±56.2 | 0.10c |
| IgG [mg/dL; mean±SD] | 894.4±240.3 | 927.0±288.0 | 0.47c |
| IgM [mg/dL; median (IQR)] | 97 (78-119) | 97 (75-136) | 0.75b |

WBC, white bood cell; CRP, C-reactive protein; IQR, interquartile range; *SD, standard deviations , **Statistically significant difference
aChi-square; bMann-Whitney test; cStudent's t test

## Discussion

To our knowledge, this study is one of the very few to focus on evaluation of recurrent fever in childhood. A major challenge in investigating recurrent fever is that the literature did not provide a definitive cut-off point regarding the frequency of febrile episodes that can be used as a threshold in diagnosing recurrent fever. For example, whereas one of the reports defined recurrent fever as the occurrence of three to four febrile episodes within a 6-month period [2], another defined it as the occurrence of 10 episodes/year during the first two to three years of

life [4]. Therefore, we defined "recurrent" fever as at least one febrile episode/month or 12 febrile episodes in a year; this was used as the cut-off point in this study.

After a long period of follow-up, it was realized that a total of three patients with recurrent fever had an underlying disease associated with fever frequency; these diseases were diagnosed with further tests. There are many disorders causing fever to recur. The autoinflammatory diseases, which are rare diseases characterized by the presence of chronic or recurrent systemic inflammation, may result in recurrent fever [5]. FMF is one of the most frequently seen. Furthermore, a large proportion of all the FMF patients in the world live in Turkey. It has a prevalence in the general Turkish population of about 0.093% [9] and mostly presents with peritonitis, fever, and arthritis [10]. In this study, one patient in Group II was diagnosed as FMF. Similarly PFAPA, which represents one of the most common type of recurrent fever in childhood, was diagnosed in one patient in 'the normal frequency fever group,' Group I. Also, congenital immune defects are one of the causes of recurrent fever in childhood, and one child had immunodeficiency in Group II in our study.

The patients who experienced 13 or more febrile episodes per year were shown to have significantly higher CRP levels. Although the factors responsible for elevation in CRP levels are unclear in the present study, it may be concluded that these children had a tendency towards infection/inflammation or towards more frequent bacterial infections, despite the fact that only six patients in our study had laboratory-confirmed bacterial infections (four urinary tract infection and two tonsillopharyngitis). In the case of infection, inflammatory disease, and trauma, acute-phase proteins like CRP, ESH, fibrinogen, and procalcitonin are involved with strong negative predictive value for inflammation [11, 12]. Rather than using these measures alone, combining them with WBC will likely yield more information with higher specificity and sensitivity [13-15].

Even healthy children may experience upper-respiratory tract system infection (URTI) three to eight times/year, particularly those who attend a day care center or school, a factor that has been associated with increased URTI [4, 16, 17]. In contrast to those reports, we did not find a significant difference in attendance at day care/school between the groups. The patients with frequent fever experienced more vomiting than the others. The patients who experienced ≤12 febrile episodes tended to experience more sneezing episodes. All of these symptoms are nonspecific and may be caused by any organ systems, although they are most commonly observed with cases of recurrent gastroenteritis, inflammatory bowel disease, meningitis, UTI, URTI, and autoinflammatory syndromes [18, 19]. As a result, careful physical examination is necessary for patients presenting with these symptoms. There was no difference between the groups according to physical examination findings, including skin eruptions, dental caries, and oral and genital ulcers. Since symptoms such as skin eruptions, oral/genital ulcers, and joint complaints may be the signs of Behçet's disease, inflammatory bowel disease, immunodeficiency, HIV infection, or periodic fever syndrome [19-21], those diseases should be considered in the differential diagnosis of patients with frequent fever.

Although several studies have reported linear growth retardation after recurrent fever and infection [22, 23], only four children in the current study had growth retardation. This can be attributed to the inadequate sample size of this study or characteristics of the patients examined, specifically having self-limiting mild episodes, absence of severe appetite loss, or experience of febrile episodes as part of periodic fever syndrome. Both infectious and non-infectious factors that induce recurrent fever may also affect liver and kidney functioning [24-26]. But, few patients in the present study had these organs involved.

Urinary tract infections have an incidence reported as up to 8.4% in studies [27, 28], as well as a high rate of asymptomatic presentation [29]. Even though there was no significant association between UTI and fever frequency in this study, recurrent fever may be caused by UTI infections that were not confirmed by laboratory tests. Hence, investigation of UTI in pediatric patients with recurrent fever is recommended. Other factors that may affect the incidence of recurrent infection are immunoglobulin levels [30]. Although none of the patients in either group had abnormal (high or low) immunoglobulin levels when compared to normal values for the same age group, one patient was diagnosed with immunodeficiency. This disorder has normal immunoglobulin levels and cannot be diagnosed unless subgroup analysis is performed. Still, testing of quantitative immunoglobulin levels remains part of the routine algorithm of recurrent fever; the decision to do further immunological tests can be made on a case-by-case basis.

Another important finding of the study was that the patients with ≤12 febrile episodes tended to experience febrile episodes more frequently in the winter season compared to other patients. This may be due to those patients having spent more time within crowded indoor places during the cold months and their increased frequency of URTI. Although several types of infections, including diarrhea-related infections, malaria, and upper- and lower-respiratory system infections have been shown to have seasonal fluctuations [31-33], to our knowledge, it is new to describe an association with recurrent fever.

Some limitations of our study should also be noted. The sample population was relatively small and only patients in outpatient clinics were enrolled. So, this may prevent further generalization of the findings. The results need to be confirmed in a larger pool. Also, patients were categorized based on reported symptoms only and not on evident illness. Additionally, the sequential analysis of infectious biomarkers to understand longitudinal changes and optimal timing for prognostic value could not be performed because of financial considerations.

In conclusion, it is known that managing patients with recurrent fever needs careful history taking, repeated physical examinations, and targeted laboratory investigations to provide potential diagnostic clues for further specified tests to reach a correct diagnosis. This study indicates that rather than determining the fever frequency (at least once a month) at admission or trying to demonstrate an algorithm for diagnosis and treatment, it would be better to execute a long term and careful follow-up to discover the etiology.

*Competing interests*

The authors declare that they have no competing interests.

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